## REMARKS/ARGUMENTS

Claims 1, 3-7, 9-13 and 16-19 are currently pending. Claims 5 and 13 are withdrawn. Claims 1, 3, 4, 6, 7, 9-12 and 16-19 are finally rejected. Applicants respectfully request reconsideration and allowance in view of the following arguments.

The claims 1, 3, 4, 6, 7, 9-11 and 16-19 stand rejected under 35 U.S.C. §102(b) as being anticipated by, or under 35 U.S.C. §103(a) as being unpatentable, over Thastrup. The claims 1, 3, 4, 6, 7, 9-12 and 16-19 stand rejected under 35 U.S.C. §103(a) as being unpatentable, over Thastrup in combination with other references. Applicants respectfully disagree. Applicants submit that Thastrup is mischaracterized and do not anticipate or render obvious the claimed invention, whether itself or combined with the cited other references.

Applicants first submit that the specification provides definitions for the key terms use in the claims. Thus, an effector is:

> *A nucleic acid sequence with biological function or activity, resulting either from an expressed protein with biological function or activity (e.g. cDNA or other coding nucleic acid sequence) or resulting from another mechanism of action (e.g. antisense and RNAi sequences).*

Lines 1-4, page 7 of the PCT application. An indicator is:

> *a nucleic acid sequence which comprises a detectable label, encodes a detectable label or which may optionally be fused to a sequence encoding a detectable protein label and expressed in a cell resulting in a characteristic localisation of the detectable protein.*

Lines 6-9, page 7. It is important to note that an indication is not simply a nucleic acid sequence which comprises a detectable label, but one that results in a characteristic localization of the detectable protein. Thus, *"[p]referably, indicator nucleic acid sequence is created by fusing the effector sequence to a nucleic acid sequence encoding a detectable label."* Paragraph bridging pages 10 and 11.

The claimed method is illustrated in Figures 3 and 4 and described in the corresponding sections of the specification. Thus, "*[t]he method of the invention may be used to establish functional relationships between genetic elements (effectors), chemical elements (modulators) and cellular assays (indicators).*" The method starts "*from collections of effectors [210] (Figure 3) and modulators [240] of known or unknown function*". In one step, indicators are generated by engineering cDNA effectors "*as fusions with a detectable marker protein [220]*". This is then "*transfected into target cells in the presence [270] and absence [260] of selected modulators [240]. Combinations of effectors, modulators and target cells giving a reproducible difference in the localisation of the detectable fusion protein are selected [S] for further rounds of functional screening in which the selected combinations are challenged with effectors [210] or modulators [240].*" Page 18, lines 4-14. Applicants submit that as illustrated by the definitions and the above cited sections, the fusion between a detectable marker and an effector constitutes the indicator, and the combination of indicators (i.e., effector-detectable marker fusion) and modulator in a cell is challenged by additional effectors – this is the focus of the present claim set.

The specification continues to described the claimed invention:

> *By this means many three-way combinations of effectors, modulators and indicators may be tested [290]. Tri-partite combinations [390] (Figure 4a) in which the activity [345] of a chemical modulator [340] and the activity [315] of a genetic effector [310] on a indicator cell based assay [360] are correlated and used to infer the presence or absence of a functional linkage [301] between effector and modulator, may be used to establish functional links and clusters between many different entities. For any collections of effectors and modulators where the biological function or activity of components of the collections are both known and unknown, and where these collections are tested in combination with indicator cell assays of a known (i.e. pre-existing assays) or unknown biological significance, eight possible three-way combinations (triplets) are possible [302]-[309], and are summarised in Table 1.*

Page 18, lines 14-26. Applicants submit it is clear from the claims and the description that three elements are included in the claimed method: an indicator, a modulator, and an effector. The indicator includes a detectable label and means to render the detectable label to result in a characteristic localization. Such means may be an effector. However, Applicants assert that the claims are clear that the indicator, although may include an effector fused with a detectable label, is a separate entity from that of the effector being assayed in step (i) of claim 1. Thus, the indicator may even include a fusion of the same effector being assayed in step (i) of claim 1, with a detectable label, as claimed in claim 9.

Applicants reiterate from the last response that Thastrup teaches using imaging to measure changes in the distribution of a luminophore, specifically GFP, within cells where the GFP is fused to a protein of known function, wherein changes in distribution of the fusion protein provides information relating to an external influence, specifically a substance having biological activity, on a cell response.

Consequently Thastrup teaches a screening method for determining the activity of a substance, typically a candidate drug, against a known biological process using a GFP fusion to a DNA sequence coding for a protein of known function. However, Thastrup teaches the use of only two components;

(i) a GFP fusion protein (e.g. PKA-GFP), which is the equivalent of the indicator in the present invention; and

(ii) a test substance (e.g. forskolin), which is the equivalent of the modulator in the present invention.

The method of Thastrup provides means to determine whether a substance having biological activity is active against a chosen known cellular process, e.g. to determine if a drug candidate compound inhibits a cellular signalling pathway which is the focus of a therapeutic program. In this aspect the method of Thastrup conforms to standard drug screening methodology, i.e. providing an assay against which multiple compounds may be individually tested in parallel for activity.

Since the method of Thastrup utilizes only two components, the function of one of which by definition has to be known, the method does not teach or motivate the method of the present invention in providing means to generate networks of functional linkages using combinations of indicators, modulators and effectors in order to assign function to an effector. No separate effector is disclosed or implied in Thastrup or any of the references cited.

Thus, Thastrup alone, or in combination with one or more cited references, do not render the claims unpatentable.

Applicants respectfully assert that the claims are in allowable form and earnestly solicit the allowance of claims 1, 3-7, 9-13 and 16-19.

Early and favorable consideration is respectfully requested.

Respectfully submitted,

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